PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 50059/009WO2	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/15325	International filing date *(day/month/year)* 02 JUNE 2000	Priority date *(day/month/year)* 04 JUNE 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 48/00; C12Q 1/00 and US Cl.: 514/44; 435/4		
Applicant DANA-FARBER CANCER INSTITUTE, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05 DECEMBER 2000	17 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer IREM YUCEL
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998) ★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/15325

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-25, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the claims:
pages 26-29, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the drawings:
pages 1-4, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-6, 8-10, 13-23	YES
	Claims	7, 11, 12	NO
Inventive Step (IS)	Claims	1-6, 8-10, 13-23	YES
	Claims	7, 11, 12	NO
Industrial Applicability (IA)	Claims	1-23	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 16-23 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest treating a condition characterized by hypoxia in a patient in a localized tissue by modifying the activity of HIF- α. The claimed invention has industrial applicability.

Claims 1-6, 8-10 and 13-15 lack novelty under PCT Article 33(2) as being anticipated by Arany et al.

Arany et al. teach that p300/CBP exerts transcrptional regulation of hypoxia regulated genes in an HIF- α dependent fashion (see figure 3). They identify compounds which modulate transcriptional responses to hypoxia by exposing the cell to the compound (externally or internally), inducing hypoxic conditions and measuring the transcriptional response of the cell (see page 12971) where the expression of a reporter gene, luciferase is assessed. Arany et al. teach that the luciferase gene is under the control of a hypoxia responsive gene element, the EPO enhancer (see page 12971). They also demonstrate the interaction of HIF-α with p300/CB or fragments thereof (see pages 12971-12972) and the role this interaction has on the transcription in hypoxic conditions.

Claims 7, 11 and 12 lack an inventive step under PCT Article 33(3) as being obvious over Arany et al. in view of Jiang et al.
Arany teaches all that is recited by the instant claims excepet for the TAD domain of HIF- α and using either deferoxamine or cobalt chloride to induce hypoxic conditions.

Jiang teach that HIF-α has 2 TADs and provide their locations. They demonstrate the transactivation activity of these TADs (see for example figure 1). They also teach the induction of hypoxic conditions using either cobalt chloride or deferoxamine (see abstract).

Thus, the ordinary artisan would have been equally motivated to use either cobalt chloride or deferoxamine to induce hypoxic (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
conditions since these are recognized equivalents (see the abstract of Jiang et al.) to the O_2 used by Arany et al. The ordinary artisan would have also recognized that like all other transactivating proteins, the TAD domains of HIF- α would have been sufficient for inducing gene expression, as exhibited by Jiang et al. Therefore the invention as a whole, would have been obvious to one of ordinary skill in the art.

Claims 1-15 meet the criteria set out in PCT Article 33(4), because the invention has industrial applicability.

---------- NEW CITATIONS ----------
NONE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/15325

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 48/00; C12Q 1/00
US CL :514/44; 435/4

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/44; 435/4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	ZHONG et al. Modulation of Hypoxia-inducible Factor 1alpha Expression by the Epidermal Growth Factor/Phosphatidylinositol 3-Kinase/PTEN/AKT/FRAP Pathway in Human Prostate Cancer Cells: Implications for Tumor Anigogenesis and Therapeutics. Cancer Research. 15 March 2000. Vol. 60, pages 1541-1545, see entire document.	1-23
Y,P	EMA et al. Molecular Mechanisms of Transcription Activation by HLF and HIF1 alpha in Response to Hypoxia: Their Stabilization and Redox Signal-induced Interaction with CBP/p300. The EMBO Journal. 1999. Vol. 18, No. 7, pages 1905-1914, see entire document.	1-23

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 27 AUGUST 2000	Date of mailing of the international search report 14 SEP 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer IREM YUCEL Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

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International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	ARANY et al. An Essential Role for p300/CBP in the Cellular Response to Hypoxia. Proceedings of the National Academy of Sciences, U.S.A. November 1996. Vol. 93, pages 12969-12973, see entire document.	1 --- 2-5, 8-18, 22
Y	EBERT et al. Regulation of Transcription by Hypoxia Requires a Multiprotein Complex that Includes Hypoxia-Inducible Factor 1, an Adjacent Transcription Factor, and p300/CREB Binding Protein. Molecular and Cellular Biology. July 1998. Vol. 18, No. 7, pages 4089-4096, see entire document.	1-23
Y	JIANG et al. Transactivation and Inhibitory Domains of Hypoxia-inducible Factor 1 alpha. The Journal of Biological Chemistry. 01 August 1997. Vol. 272, No. 31, pages 19253-19260, see entire document.	1-23
Y	KALLIO et al. Signal Transduction in Hypoxic Cells: Inducible Nuclear Translocation and Recruitment of the CBP/p300 Coactivator by the Hypoxia-inducible Factor 1 alpha. The EMBO Journal. 1998. Vol. 17, No. 22, pages 6573-6586, see entire document.	1-23
Y	BHATTACHARYA et al. Functional Role of p35srj, a Novel p300/CBP BInding Protein During Transactivation by HIF-1. Genes and Development. 1999. Vol. 13, pages 64-75, see entire document.	1-23
Y,P	NEWTON et al. The Transactivation Domain within Cysteine/Histidine-rich Region 1 of CBP Comprises Two Novel Zinc-binding Modules. The Journal of Biological Chemistry. 19 May 2000. Vol. 275, No. 20, pages 15128-15134, see entire document.	1-23
Y	US 5,658,784 A (ECKNER et al.) 19 August 1997(19.08.97), see entire document.	1-23

INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

WEST, STN, DIALOG, Caplus, Medline, Biosis, Scisearch, Derwent, Pascal

Terms: inventors' names, hypox?, oxygen?, reduc?, deplet?, lower, decreas?, control?, attenuat?, p300, creb binding protein, CBP, HIF, hypoxia induc?, factor? CH1, test?, screen? modulat?